REMARKS

Claims 1-40 are currently pending. Claims 6, 10-13, 21, 25-28, 33 and 37-40 are withdrawn without prejudice to their rejoinder in this application or prosecution in another application. Claims 1, 14 and 29 are amended to more clearly describe the claimed subject matter. The amendments are supported for example at page 1, lines 22-23, and 30-32; and page 19, lines 15-18 of the specification as filed.

The Examiner has maintained the rejection of claims 1-5, 7-9, 14-17, 19, 20, 22-24, 29-32 and 34-37 under 35 U.S.C. § 103(a) as being unpatentable over Yew et al. (U.S. Patent 6,066,626 to Yew et al.) ("Yew et al.") in view of Fan '597 (U.S. Patent 6,274,597 to Fan et al.) ("Fan '597"). The Examiner has maintained the rejection of claims 1-5, 7-9, 14-17, 19, 20, 22-24, 29-32 and 34-37 under 35 U.S.C. § 103(a) as being unpatentable over Yew et al. in view of Fan '964 (U.S. Patent 6,589,964 to Fan et al.) ("Fan '964"), Fan '919 (U.S. Patent 6,599,919 to Fan et al.) ("Fan '919") and Fan '135 (U.S. Patent 6,774,135 to Fan et al.) ("Fan '135"). The Examiner has maintained the rejection of claims 17 and 18 under 35 U.S.C. § 103(a) as being unpatentable over Yew et al. in view of Fan '597, and further in view of Hendricks et al. (Hendricks et al., 2000, Blood 96(11 part 1):845a). Finally, the Examiner has maintained the rejection of claims 17 and 18 under 35 U.S.C. § 103(a) as being unpatentable over Yew et al. in view of Fan '964, Fan '919 or Fan '135, and further in view of Hendricks et al. For the reasons detailed below, the rejections should be withdrawn and the claims allowed to issue.

I. Examiner Interview

Applicant thanks the Examiner for participating in an interview on August 14, 2007, with the undersigned and Dennis Bissonnette. During the interview, Applicant noted that the proviso added in the March 5, 2007 Amendment was meant to refer to the individual's endogenous protein. The Examiner noted that such an amendment would appear to overcome the obviousness rejections.

II. The Claims Are Not Obvious

A. The claims are not obvious over Yew et al. in view of Fan '597

Claims 1-5, 7-9, 14-17, 19, 20, 22-24, 29-32 and 34-37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Yew et al. in view of Fan '597. According to the Examiner, Yew et al. describes methods of providing biologically active human alpha galactosidase A to cells of an individual having a deficiency of the enzyme (Fabry's disease) by administering a recombinant gene encoding the enzyme in an adenoviral expression construct to cells of the individual, and further, that administration of the recombinant gene may be done *in vivo* or *ex vivo*. The Examiner contends that Fan '597 describes methods of increasing the activity of alpha galactosidase A with competitive inhibitors of alpha galactosidase A, and methods of treating Fabry's disease by increasing the activity of mutant lysosomal alpha galactosidase A in mammalian cells by administering an effective amount of the alpha galactosidase A inhibitor 1-deoxygalactonojirimycin.

The Examiner alleges that it would have been obvious to one skilled in the ordinary art to combine the gene therapy methods of Yew et al. with the active-site specific chaperone (ASSC)

methods of Fan '597. According to the Examiner, the combination of Yew et al. and Fan '597 describes the claimed invention.

Applicant respectfully disagrees with the Examiner. To establish a *prima facie* case of obviousness, all the claim limitations must be taught or suggested by the prior art (*In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494,496 (C.C.P.A. 1970) states that "[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art." The Examiner must also meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*See* PTO interim guidelines[1]); (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See M.P.E.P. §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, rather than Applicants' disclosure.

There is no motivation to combine the teachings of Yew et al. and Fan '597, and further, there is no reasonable expectation of success by combining the references in view of the presently amended claims. The amended claims are directed to methods of improving gene therapy in individuals whose protein deficiency is such that pharmacological chaperone-based therapy on its own would have no meaningful effect. Instead, the expression-enhancing effects of pharmacological chaperones are claimed in the context of the ability to enhance expression of a therapeutic protein encoded by a therapeutic recombinant gene. The claims have been amended to recite "with the proviso that the individual's endogenous protein is not a mutant,

[1] Memorandum regarding the Supreme Court decision on *KSR Int'l. Co., v. Teleflex, Inc.*, from Margaret A. Focarino, Deputy Commissioner for Patent Operations, USPTO, to Technology Center Directors (May 3, 2007).

endogenous protein that is deficient due to defective folding or processing in the endoplasmic reticulum." This is contrary to the situation where the amount of protein expressed is potentially sufficient, but because it fails to traffic to the correct cellular location, it does not perform its function. An individual's endogenous protein may be deficient due to both genetic and non-genetic factors (page 1, lines 30-32). For example, a mutation in the coding region of a gene may result in non-synthesis of the protein (page 1, lines 22-23). Alternatively, the level or amount of protein may be insufficient for biological activity due to "disease, or as a side effect of a treatment for a disease (e.g., chemotherapy) or as a result of nutritional insufficiency" (page 1, lines 30-32).

Conditions such as "infectious diseases, immunosuppression, organ failure, glandular problems, radiation illness, nutritional deficiency, poisoning, or other environmental or external insults" may result in insufficient levels of endogenous protein for biological function (page 9, lines 27-29). When environmental or external insults are responsible for the protein deficiency, the individual's gene encoding the protein may not contain any genetic mutations. The protein encoded by the gene may retain normal wild type activity, but the environmental or external insult prevents the protein from reaching levels of expression sufficient to achieve normal biological function. For example, damage to the pancreas, caused by alcoholism (pancreatitis), results in a deficiency of pancreatic enzymes necessary for digestion (page 19, lines 15-18). The pancreatic cells encode and express functional pancreatic enzymes, but the level of enzymes expressed is insufficient for biological function since the tissue producing the enzymes has been damaged.

Applicant asserts that the presently amended claims are not obvious in view of the cited art. As stated by the Examiner in the Final Office Action issued October 4, 2006, "one of skill in

the art understands that chaperone therapy is only applicable to situations in which a mutant protein can be refolded and would act accordingly . . ." (page 11, lines 8-10 of the October 4, 2006, Final Office Action). Conformational disorders result from "mutations that alter protein folding and retardation of the mutant protein in the ER" (page 14, lines 24-26 of the specification). Conformational mutant phenotypes do not manifest because the proteins are expressed at an insufficient level, but because once expressed, the proteins adopt an inactive conformation, triggering their degradation and preventing the enzymes from interacting with their substrates. Distinct from conformational disorders, the presently amended claims encompass individuals with protein deficiencies caused by, for example, reduced levels of a protein, or the absence of the protein altogether. It would not have been obvious to use chaperone therapy to treat these individuals since a skilled artisan would only look towards chaperone therapy when a condition to be treated is associated with a misfolded protein. Thus, there would be no motivation to combine the teachings of Yew et al. with Fan '597. Furthermore, one skilled in the ordinary art, with Yew et al. and Fan '597 in hand, would not reasonably expect the method of Fan '597 to succeed in treating an individual who expresses an insufficient level of a properly folded protein, or no protein at all, as encompassed by the present claims. Applicant therefore asserts that the presently amended claims are not obvious and requests that the rejection be withdrawn.

B. The claims are not obvious over Yew et al. in view of Fan '964, Fan '919 or Fan '135

Claims 1-5, 7-9, 14-17, 19, 20, 22-24, 29-32 and 34-37 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Yew et al. in view of Fan '964, Fan '919 or Fan '135. According to the Examiner, the Fan patents constitute prior art under 102(e) based upon the

effective U.S. filing dates of the references. As discussed above, the Examiner contends that Yew et al. is directed to methods of gene therapy for treating alpha galactosidase A deficiencies. The Examiner also alleges that Fan '964 describes methods of enhancing the activity of an enzyme in a mammalian cell line by administering a competitive inhibitor of the enzyme, and further, that Fan '964 discloses methods of increasing the activity of mutant alpha galactosidase A in mammalian cell lines, and treating Fabry's disease in an individual by administering an effective amount of 1-deoxygalactonojirimycin.

The Examiner alleges that Fan '919 discloses methods of enhancing the activity of an enzyme in a mammalian cell, wherein the enzyme, when mutated, tends to fold in an incorrect conformation in the ER, and whereby a level of the active enzyme is deficient as a result of such mutation. According to the Examiner, the described methods include increasing the activity of the mutant enzyme, and the treatment of glycosphingolipid storage disease by administering a competitive inhibitor of the enzyme such as 1-deoxygalactonojirimycin.

The Examiner contends that Fan '135 describes methods of treating Fabry's disease comprising administering an effective amount of 1-deoxygalactonojirimycin to an individual in need of treatment.

According to the Examiner, it would have been obvious to one skilled in the ordinary art to treat an individual with Fabry's disease by administering both the gene therapy constructs of Yew et al. and 1-deoxygalactonojirimycin. The Examiner contends that one would have been motivated to combine Yew et al. with any one of the teachings of Fan '919, Fan '135, or Fan '964 in order to supplement the wild type protein of Yew et al. with an increase in endogenous protein activity as described in the Fan references.

In the Response to Final Office Action filed June 8, 2006, Applicant provided copies of filing receipts, issue fee transmittals, application data sheets, provisional application cover sheets, and/or Notice of Recordation forms demonstrating that the three Fan patents, as well as the instant application, were commonly owned by the Mount Sinai School of Medicine of New York University at the time the present invention was made, thus excluding the cited references as prior art for obviousness rejections (*see* U.S.C. § 103(c)). In the Advisory Action issued June 21, 2006, the Examiner stated that Applicant has overcome the obviousness rejections based on any one of U.S. Patent Nos. 6,589,964, 6,599,919 or 6,774,135. Thus Applicant requests that the rejection be withdrawn.

C. The claims are not obvious over Yew et al. in view of Fan '597 and Hendricks et al.

Claims 17 and 18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Yew et al. in view of Fan '597 and Hendricks et al. As previously described, the Examiner contends that Yew et al. is directed to methods of gene therapy to treat protein deficiency disorders, while Fan '597 relates to methods of chaperone therapy for treating protein deficiency disorders. According to the Examiner, Hendricks et al. describes methods in which human mesenchymal stem cells are transduced with a retroviral expression vector encoding alpha galactosidase A, and then implanted into mice where they secrete high levels of alpha galactosidase A.

The Examiner contends that it would have been obvious to combine the gene therapy of Yew et al. and the chaperone therapy of Fan '597 with the mesenchymal stem cells of Hendricks et al., wherein the mesenchymal stem cells serve as the gene delivery vehicle for Yew et al.'s gene therapy constructs, and express alpha galactosidase A at high levels.

Applicant respectfully disagrees. As stated previously, there would be no reasonable expectation of success, and no motivation to combine the gene therapy of Yew et al. with the chaperone therapy of Fan '597 since a skilled artisan would only look to chaperone therapy as a method for treating a disorder resulting from misfolded and inactive protein conformations. The presently amended claims are directed to treating protein deficiencies resulting from absent, or an insufficient amount, of an endogenous protein for biological function, not misfolded proteins. The absence or insufficiency can result from genetic defects, environmental, or external insults. Because an artisan of ordinary skill would have no motivation to combine the references with a reasonable expectation of success, Applicant requests that the rejection be withdrawn.

D. The claims are not obvious over Yew et al. in view of Fan '964, Fan '919 or Fan '135 and further in view of Hendricks et al.

Claims 17 and 18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Yew et al. in view of Fan '964, Fan '919 or Fan '135, and further in view of Hendricks et al. As disclosed above, the Examiner contends that Yew et al. relates to methods of gene therapy treatment; the Fan references are directed to the use of chaperone therapy to treat protein folding disorders; and Hendricks et al. discloses methods of using mesenchymal stem cells to express a vector encoding alpha galactosidase A, and further, implanting the cells into a subject.

The Examiner contends that it would have been obvious to combine the gene therapy of Yew et al. and the chaperone therapy of any one of the Fan references with the mesenchymal stem cells of Hendricks et al., wherein the mesenchymal stem cells serve as the gene delivery vehicle for Yew et al.'s gene therapy constructs, and express alpha galactosidase A at high levels.

Fan '964, '919 and '135, along with the instant application, were commonly owned at the time the instant invention was made. Thus, the Fan patents are disqualified as prior art under §103(a) against the claimed invention. As such, the Examiner stated in the June 21, 2006 Advisory Action, that obviousness rejections based on these three Fan patents had been overcome. Applicant therefore requests that the rejection be withdrawn.

III. Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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Enclosures